



Mr. Anil Hiteshi, RAC,
Vice President, Global Regulatory Affairs
Spectrum Pharmaceuticals
157 Technology Drive
Irvine, CA 92618

RE: BLA #125019
ZEVALIN[®] (ibritumomab tiuxetan) Injection for Intravenous Use
MA #195

Dear Mr. Hiteshi:

As part of its routine monitoring and surveillance program, the Office of Prescription Drug Promotion (OPDP), of the U.S. Food and Drug Administration (FDA) has reviewed a professional sales aid (0103058300) (sales aid) for ZEVALIN[®] (ibritumomab tiuxetan) Injection for Intravenous Use (Zevalin) submitted by Spectrum Pharmaceuticals, Inc. (Spectrum) under cover of Form FDA 2253. This sales aid is false or misleading because it minimizes important risk information, overstates the efficacy of Zevalin, and omits material facts. Thus, the sales aid misbrands Zevalin in violation of the Federal Food, Drug, and Cosmetic Act (the FD&C Act), 21 U.S.C. 352(a) & 321(n), and implementing regulation 21 CFR 1.21(a). Cf. 21 CFR 202.1(e)(5)(i), (iii); (e)(6)(i), (x), (xviii).

Background

Below is the indication and summary of the most serious and most common risks associated with the use of Zevalin.¹ According to the FDA-approved product labeling (PI), Zevalin is indicated for the treatment of patients with:

- Relapsed or refractory, low-grade or follicular B-cell non-Hodgkin's lymphoma (NHL)
- Previously untreated follicular NHL who achieve a partial or complete response to first-line chemotherapy

Zevalin is associated with a number of serious risks, many of which are potentially fatal. The Zevalin PI contains Boxed Warnings for serious infusion reactions, prolonged and severe cytopenias, severe cutaneous and mucocutaneous reactions, and dosing limitations for radiation exposure. The PI also contains Warnings and Precautions regarding altered biodistribution, leukemia and myelodysplastic syndrome, embryo-fetal toxicity, extravasation, immunization, laboratory monitoring, radionuclide precautions, and Creutzfeldt-Jakob Disease (CJD).

¹ This information is for background purposes only and does not necessarily represent the risk information that should be included in the promotional piece cited in this letter.

As stated in the PI, the most common adverse reactions associated with Zevalin are cytopenias, fatigue, nasopharyngitis, nausea, abdominal pain, asthenia, cough, diarrhea, and pyrexia.

Prior Communications with OPDP

OPDP is concerned that the violative conduct described above occurred despite repeated OPDP advisory comments addressing similar misleading presentations dated August 15, 2003, February 19, 2004, December 27, 2004, May 18, 2006, and November 6, 2009. Among other concerns, OPDP recommended that Spectrum eliminate presentations that mischaracterize the mechanism of action and minimize the risks, omit material facts, and overstate the efficacy of Zevalin. We are concerned that Spectrum is continuing to promote Zevalin in a violative manner despite clear direction from OPDP.

Minimization of Risk Information

Promotional materials are misleading if they contain claims that a drug is safer than has been demonstrated by substantial evidence or substantial clinical experience. The front cover of the sales aid includes a picture of an archer taking aim at a target populated with lymphoma cells. The “arrow” being drawn back by the archer represents the Zevalin drug product, and shows standard imagery depicting a monoclonal antibody linked to a radioactive isotope. This imagery is repeated throughout the sales aid at the top of each two-page spread. On the back cover of the sales aid, the arrow is shown lodged within the lymphoma cells in the center of the target. This imagery misleadingly suggests that Zevalin can precisely target lymphoma cells without targeting healthy cells. Additionally, page seven of the sales aid includes the following claims (emphasis added):

- “ZEVALIN **delivers radiation precisely** where it’s needed”
- “Monoclonal antibody **specifically** targets the CD20 antigen found on **95%** of B-cell lymphomas.^{2,3}”

The references cited to support these claims include a phase I/II study for Zevalin as well as the Zevalin PI, neither of which support claims that Zevalin can selectively target lymphoma cells. The objective of the phase I/II study was to determine the maximum tolerated single dose of Zevalin that could be administered without stem cell support and does not support claims of selective targeting of lymphoma cells. Furthermore, according to the MECHANISM OF ACTION section of the Zevalin PI:

Ibritumomab tiuxetan binds specifically to the CD20 antigen The CD20 antigen is expressed on pre-B and mature B lymphocytes and on >90% of B-cell non-Hodgkin’s lymphomas The beta emission from Y-90 induces cellular damage by the formation of free radicals in the target and neighboring cells.

Given that CD20 is also expressed on non-malignant B-cells, any claims or presentations

² ZEVALIN [package insert]. Irvine, CA: Spectrum Pharmaceuticals, Inc.

³ Witzig TE, White CA, Wiseman GA, et al. Phase I/II trial of IDEC-Y2B8 radioimmunotherapy for treatment of relapsed or refractory CD20+ B-cell non-Hodgkin’s Lymphoma. *J Clin Oncol.* 1999; 17(12): 3793-3803.

that suggest that Zevalin selectively targets lymphoma cells are misleading. Moreover, as stated in the PI, the Y-90 covalently bound to ibritumomab emits beta radiation particles that have a range of 5 mm. These beta emissions can induce cellular damage in *all* cells within this range. By indicating that Zevalin is specifically targeted to lymphoma cells, the archer imagery throughout the sales aid and the claims on page seven minimize the serious risks that Zevalin presents to patients as a result of its destruction of healthy cells and tissues. These risks include prolonged and severe cytopenias, secondary malignancies, as well as radiation injury to tissues near areas of lymphomatous involvement.

Pages 13 and 19 of the sales aid include the following misleading headers (emphasis added):

- “Grade 3 / 4 hematological side effects in relapsed or refractory patients can be **predictable and manageable**” (page 13)
- “Grade 3 / 4 hematological side effects in patients following first-line induction chemotherapy can be **predictable and manageable**” (page 19)

Describing the hematological side effects of Zevalin as “predictable and manageable” minimizes these serious risks. According to the WARNINGS AND PRECAUTIONS section of the Zevalin PI:

Cytopenias with delayed onset and prolonged duration, some complicated by hemorrhage and severe infection, are the most common severe adverse reactions of the Zevalin therapeutic regimen...Severe cytopenias persisting more than 12 weeks following administration can occur.

OPDP notes the asterisked disclosure on these pages which states, “Severe cytopenias persisting more than 12 weeks following administration can occur.” However, the inclusion of this information is not sufficient to mitigate the overwhelming misleading impression conveyed by the headers on these pages.

Overstatement of Efficacy

Promotional materials are false or misleading if they represent or suggest that a drug is more effective than has been demonstrated by substantial evidence or substantial clinical experience.

Page four of the sales aid includes a presentation of overall survival data and makes the following misleading claims:

- “Patients reaching complete response after first-line treatment are more likely to experience improved overall survival⁴”
- “Patients achieving a complete response had improved long-term survival versus patients who experienced a partial response (PR) at any time during the study period”

⁴ Bachy E, Brice P, Delarue R, et al. Long-term follow-up of patients with newly diagnosed follicular lymphoma in the prirituximab era: effect of response quality on survival-a study from the Groupe d'Etude des Lymphomes de L'Adulte. *J Clin Oncol*. 2009; 28(5): 822-829.

- “Data from this study suggest a strong correlation between response quality after first-line treatment (complete response) and survival”

In the context of this sales aid for Zevalin these claims misleadingly overstate the efficacy of the product by implying that Zevalin has demonstrated efficacy in terms of overall survival when used after first line treatment, when this is not the case. In fact, the study supporting approval of Zevalin following first-line induction (Study 4 in the PI) failed to show any improvement in overall survival for patients treated with Zevalin as compared to those who received no further treatment. The reference cited in support of these claims, the 2010 study by Bachy, et al., contains data evaluating the effects of response quality on survival for patients in the pre-rituximab era and does not contain any data evaluating Zevalin on any efficacy endpoint. We note the disclaimer at the bottom of the page which states, “ZEVALIN (ibritumomab tiuxetan) treatment regimen is NOT indicated for first-line treatment in previously untreated follicular lymphoma patients prior to chemotherapy. There are no FDA approved clinical data comparing the efficacy of ZEVALIN to R-maintenance;” however, this statement does not mitigate the misleading impression that Zevalin can improve survival as suggested by the inclusion of overall survival claims in this sales aid.

Pages 10 and 11 of the sales aid contain the following misleading claims:

- **“Earlier treatment with ZEVALIN treatment regimen was shown to provide benefits”**
- “Earlier treatment with ZEVALIN may improve ORR⁵”
- “In patients with ORR after first relapse, ZEVALIN may improve median time to progression (TTP)⁵”
- “Median TTP was 12.6 months in patients at first relapse versus 7.9 months in patients at second or subsequent relapse (P=0.025).”
- “Earlier treatment with ZEVALIN nearly doubled CR/CRu rates⁵”
- “In patients with a CR/CRu after first relapse, ZEVALIN may improve median time to progression⁵”

These claims are presented with several bar graphs comparing overall response rate (ORR), complete response rate (CR/CRu), and median time to progression (TTP) in patients treated with Zevalin after first relapse versus patients treated with Zevalin after second or subsequent relapse. These claims of enhanced efficacy with “earlier treatment” using Zevalin are misleading because they are not supported by substantial evidence or substantial clinical experience. The reference cited in support of these claims, a study by Emmanouilides C, et al. did not evaluate earlier versus delayed initiation of treatment in patients at the same time point in disease course (e.g., at first, second, third relapse, etc.). Rather, the study involved a retrospective comparison of outcomes between different patient populations. Conclusions about the therapeutic effect of a drug cannot be drawn by comparing outcomes between different patient populations. This retrospective comparison does not constitute substantial evidence to support any benefit or efficacy claims related to “earlier” treatment with Zevalin. Moreover, the claims fail to account for the fact that higher ORR, CR/CRu, and TTP achieved by patients in first relapse compared to multiple relapsed

⁵ Emmanouilides C, Witzig TE, Gordon L, et al. Treatment with yttrium 90 ibritumomab tiuxetan at early relapse is safe and effective in patients with previously treated B-cell non-Hodgkin's lymphoma. *Leuk Lymphoma*. 2006; 47(4): 629-636.

patients is expected and attributable to the natural course of the disease.

Pages 14 and 15 of the sales aid present four pie charts that compare the changes in CR/CRu and PR rates, or “PR to CR/CRu conversion rate” for patients in the two arms of Study 4 before and after the clinical trial. The pie charts show an improvement in CR/CRu rate from 51% before the trial to 87% after consolidation therapy with Zevalin. In the control arm, CR/CRu rates remained steady at 53%. These pie charts are misleading because they suggest that consolidation therapy with Zevalin has proven efficacy in terms of enhanced CR rates for patients who had a response after first-line induction therapy, when this has not been demonstrated by substantial evidence or substantial clinical experience. The references cited in support of these claims include the Zevalin PI and the publication of the Study 4 trial results by Morschhauser F, et al.⁶, neither of which supports claims related to improvements in CR rate. Analysis of improvement of CR rate was not a pre-specified secondary endpoint in Study 4. These claims are based on a post-hoc, exploratory subgroup analysis of the trial data and confounded by frequent discrepancies in the PR and CR/CRu determinations made by the investigators. This type of analysis does not provide substantial evidence to support efficacy claims related to PR to CR/CRu conversion rate.

Omission of Material Fact

Promotional materials are misleading if they fail to reveal facts that are material in light of the representations made.

Page eight of the sales aid includes the following misleading claim:

- “ZEVALIN patients experienced a median time to progression of 12.1 months vs. 10.1 months for rituximab patients”

This claim is misleading as it omits important material information regarding the statistical significance of the time to progression data. Specifically, as stated in the PI: “Time-to-disease-progression was not significantly different between study arms.”

Conclusion and Requested Action

For the reasons discussed above, the sales aid for Zevalin misbrands the drug in violation of the FD&C Act, 21 U.S.C. 352(a) & 321(n), and implementing regulation 21 CFR 1.21(a). Cf. 21 CFR 202.1(e)(5)(i), (iii); (e)(6)(i), (x), (xviii).

OPDP requests that Spectrum Pharmaceuticals, Inc. immediately cease the dissemination of violative promotional materials for Zevalin such as those described above. Please submit a written response to this letter on or before August 6, 2013, stating whether you intend to comply with this request, listing all promotional materials (with the 2253 submission date) for Zevalin that contain violations such as those described above, and explaining your plan for discontinuing use of such violative materials.

⁶ Morschhauser F, Radford J, Van Hoof A, et al. Phase III trial of consolidation therapy with yttrium-90-ibritumomab tiuxetan compared with no additional therapy after first remission in advanced follicular lymphoma. *J Clin Oncol*. 2008; 26(32): 5156-5163.

Please direct your response to the undersigned at the **Food and Drug Administration, Center for Drug Evaluation and Research, Office of Prescription Drug Promotion, 5901-B Ammendale Road, Beltsville, Maryland 20705-1266** or by facsimile at (301) 847-8444. To ensure timely delivery of your submissions, please use the full address above and include a prominent directional notation (e.g., a sticker) to indicate that the submission is intended for OPDP. Please refer to MA #195 in addition to the BLA number in all future correspondence relating to this particular matter. OPDP reminds you that only written communications are considered official.

The violations discussed in this letter do not necessarily constitute an exhaustive list. It is your responsibility to ensure that your promotional materials for Zevalin comply with each applicable requirement of the FD&C Act and FDA implementing regulations.

Sincerely,

{See appended electronic signature page}

Kathleen Davis, RN
Regulatory Review Officer
Office of Prescription Drug Promotion

{See appended electronic signature page}

Karen Rulli, Ph.D.
Team Leader
Office of Prescription Drug Promotion

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/s/

KATHLEEN T DAVIS
07/23/2013

KAREN R RULLI
07/23/2013